NORTH AMERICAN POLYELECTROLYTE PRODUCERS ASSOCIATION

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Dr. Michael Shelby, Director
Center for the Evaluation of Risks to Human Reproduction (CERHR)
National Institute of Environmental Health Sciences (NIEHS)
P.O. Box 12233, MD EC–32
Research Triangle Park, NC 27709
Via E-mail: shelby@niehs.nih.gov

Re: Comments on CERHR Expert Panel Report on Acrylamide

Dear Dr. Shelby:

The North American Polyelectrolyte Producers Association (NAPPA) welcomes the opportunity to comment on the NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Acrylamide dated June 2004 (NTP-CERHR-Acrylamide-04) as announced in the *Federal Register* on June 21, 2004 (69 *Fed. Reg.* 34382). NAPPA represents the major manufacturers and importers of synthetically produced coagulants and flocculants, which are generically referred to as polyelectrolytes. A major class of these polyelectrolytes is polyacrylamides. Some of NAPPA's members not only produce these polyacrylamides, but they are also manufacturers of the acrylamide monomer. For this reason, NAPPA members have a unique interest in this report and as such have been actively involved in this proceeding.

Generally, the summaries of the results of individual toxicity studies are accurate. However, the conclusions require comment particularly relating to the issues of occurrence of neurotoxicity in the workplace and industrial exposure. The Report states that:

> *Recognizing the broad range of occupational exposure estimates for acrylamide, the occurrence of neurotoxicity in some occupational settings, and the concurrent expression of neurotoxicity and reproductive toxicity in some experimental animal studies, the Expert Panel expressed some concern for adverse reproductive and developmental effects, including heritable effects, for exposures in occupational settings.*

Briefly, there have been no reported cases of neurotoxicity due to workplace exposure to acrylamide in the United States in the past two decades. Exposure is overestimated in the report by more than a factor of 10, the LOAEL in the rodent developmental study was 2.5-fold lower than the reproductive LOAEL (*i.e.*, there were no reproductive effects observed at doses which did not also induce maternal toxicity)

and neurotoxicity is a more sensitive endpoint than reproductive toxicity. Each of these issues is briefly described below.

Industrial Exposure

In Table 37 of the Report, the upper 90th percentile for industrial exposure is given as 45-52 µg/kg bw/day. We are unable to ascertain the source of this value. Within the United States, the OSHA PEL is 0.3 mg/m^3. Consequently, air concentrations of acrylamide do not exceed this value. Facilities are designed to operate substantially below 0.3 mg/m^3 to comply with the workplace regulations. In order to permanently operate within the regulations, the mean value must be maintained at or around 0.1 mg/m^3. The ACGIH TLV is even lower at 0.03 mg/m^3. The majority of states within the US utilize this TLV as a standard. It is also recognized internationally.

To attain the body burden exposure level of 45 µg/kg bw/day cited above, employees would necessarily be exposed to air levels of greater than 0.3 mg/m^3:

$$(45\text{-}52\ \mu g\ AM/kg\ bw/day) \times (70\ kg\ bw) = 3{,}150\text{-}3{,}650\ \mu g/day.$$

At a working inhalation rate of 10 m^3 for an 8-hour shift, this would result in air concentrations between 0.32 to 0.36 mg/m^3.

Internal Dose

Since acrylamide is absorbed at 50% or less by the inhalation route[1] and at 5% or less by the dermal route[2], the air concentrations required to attain the exposure given in Table 37 would exceed the OSHA PEL by a factor of 2, *i.e.*, 0.65 to 0.7 µg/m^3.

Additionally, since there are only 200 workdays per year, the value would be even higher at 1.19 to 1.28 µg/m^3. Based on the workplace exposure value given in the final report, more than 10% of the workforce is exposed to air concentrations that are four times higher than the OSHA standard and are in violation of the Occupational Safety and Health Act, not to mention the ACGIH TLV of 0.03 mg/m3. This estimate is flawed and needs revision. Additionally, the estimates of the upper 90th percentile are too high. Based on current, industry-wide practices, air levels approximating 0.09 mg/m^3 are more representative of the upper 90 percentile. This value is in agreement with the geometric mean reported in the EU Risk Assessment for UK where the MEL is 0.3 mg/m^3. The value for Germany was much lower and that for the Netherlands included the values for the manufacture of solid grade acrylamide. The manufacture of solid grade acrylamide,

[1] Sumner, S.C.J., Asgharian, B., Williams, C.C. and Fennell, T.R. (2001) Acrylamide: Metabolism, Distribution, and Hemoglobin Adducts in Male F344 Rats and B6C3F1 Mice Following Inhalation Exposure and Distribution and Hemoglobin Adducts Following Dermal Application to F344 Rats. CIIT report to Polyelectrolyte Producers Group (PPG).

[2] Fennell, T., Sumner, S.J., Snyder, R.W., Burgess, J., Spicer, R., Bridson, W.E. and Friedman, M.A. (In Press) Metabolism and Hemoglobin Adduct Formation of Acrylamide in Humans. *Tox. Sci.*

which produces air levels far higher than are generated from liquid acrylamide, does not take place in United States.

With regard to dermal absorption, I am enclosing a manuscript describing the research from which the Cosmetic Ingredient Review (CIR) Expert Panel generated their value for dermal absorption. Briefly stated, humans absorb approximately 5% of applied dose over a 24-hour period of continuous exposure. Over an 8-hour workday this would result in (5% × 8) / 24 = 1.67% of any acrylamide contacted dermally being absorbed. The Report's worst-case calculations are based on assumed dermal and inhalation absorption of 100%. We encourage CERHR to rely on the experimental data.

The Report expresses some confusion over the estimates of exposure from the Sumner papers. These are semantic difficulties. In the case of Dr. Sumner's higher estimate (22%), she evaluated material that was not recoverable from the dosing solution. In the case of her lower estimate (2%), she measured the systemically available dose. We believe that systemic dose should be the relevant metric.

Grouting has historically been an area of concern. There are recent data that bear on the issue of exposure among grout workers. We are providing a copy of a recent study conducted by Dr. Leonard Vance of Virginia Commonwealth University. In this study, he evaluates acrylamide exposure among grout workers in Maryland. He finds virtually no exposure among these workers. There are two reasons for this: there is an increased awareness of the potential adverse health effects of acrylamide; and, a different physical form of acrylamide was supplied, which results in lower exposure. There has been no reported neurotoxicity as a result of grout use in the US in the last two decades.

With regard to exposures in developing countries, technology has improved also. The toxicological properties of acrylamide have been disseminated and there are no documented overexposures as identified in the reports from Dr. Costa's group in China.

Developmental Effects

The Report describes a large number of negative developmental toxicity studies. There were some studies where clear maternal toxicity was accompanied by lower body weights in the pups, which is not unexpected due to effects on water consumption and behavioral parameters. However, the document should conclude that at doses where there is no maternal toxicity, there are no developmental effects. The cause of these developmental effects is not relevant as maternal toxicity would be present. While of academic interest, developmental effects do not impact on the thrust of the document.

Reproductive Toxicity versus Neurotoxicity

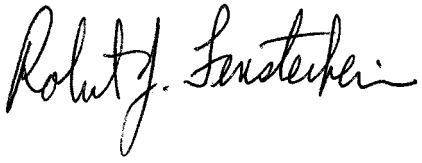
The LOAEL for reproductive toxicity, cited in the report, is 5 to 8 mg/kg/day (the basis for citing 8 mg/kg/day is unclear as this dose level was not used in the study. In this study, neurotoxicity (leg splay) was observed at the 2.0 and 5.0 mg/kg/day groups in parental and F_1 generations in this reproduction study with LOAEL of 0.5 mg/kg/day. The LOAEL for neurotoxicity in a 13-week study was 1 mg/kg/day with a NOAEL of 0.2 mg/kg/day. Neurotoxicity is clearly a more sensitive endpoint. The statement that the neurotoxic and reproductive effects occur concurrently refers to highly neurotoxic doses. Relevant arguments can be made mechanistically to support this contention, but these mechanistic arguments take away from the toxicological data sited in the report.

Conclusion

Industrial exposure has been overstated in the CERHR Expert Panel Report. Moreover, the conclusions are based on the concurrent observation of neurotoxicity and reproductive effects, which are not relevant to the relative potency. Based on an air level of 0.09 mg/m^3, the annualized daily exposure would be 0.49 mg/person/day (0.09 mg/m^3 $\times$ 10 m^3/day $\times$ 200 days worked/365 days per year) or 0.007 mg/kg bw/day. This is approximately 1,000-fold less than the LOAEL and 350 fold lower than the NOAEL. It is also 71 fold lower than the NOAEL for neurotoxicity. The exposure of 0.007 mg/kg/day is approximately 10 fold higher than the exposure from food. However, Erdreich[3] demonstrated that lifetime exposure from food was equivalent to lifetime industrial exposure as measured by Marsh *et al.*[4]

Based on the above cited data, we recommend that the CERHR conclusion mirror the EU conclusion that "an adequate margin of safety exists for the protection of workers from the reproductive effects of acrylamide."

Sincerely,



Robert J. Fensterheim
Executive Director

[3] Erdreich, L.S. and Friedman, M.A. (2004) Epidemiologic Evidence for Assessing the Carcinogenicity of Acrylamide. *Regul. Toxicol. Pharmacol.* 39(2): 150-157.

[4] Marsh, G.M., Lucas, L.J., Youk, A.O. and Schall, L.C. (1999) Mortality Patterns Among Workers Exposed to Acrylamide: 1994 Follow Up. *Occupational and Environmental Medicine* 56: 181-190.